Multi-objective Optimization and Feedback-based Chemotherapy Drug Scheduling

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***Abstract*—Cancer is a major global health issue, causing significant suffering and deaths worldwide. To minimize the adverse effects of cancer and optimize the effectiveness of chemotherapy, the implementation of chemotherapy dose scheduling procedures is necessary for treatment. By administering the proper amount of chemotherapy drug dose, the treatment can maintain optimal therapeutic levels in the body while providing enough period for healthy cells to recover. Furthermore, cell cycle-specific chemotherapy enhances treatment outcomes by targeting dividing cancer cells at specific cell cycle phases, resulting in improved efficacy and reduced toxicity to normal cells. This study proposes a novel approach combining a multi-objective particle swarm optimization (MOPSO) with a feedback generator to develop a cell cycle-specific chemotherapy drug dose scheduling system. The multi-objective optimization algorithm considers conflicting objectives such as targeting cancerous cells, preserving normal cells, and minimizing toxicity. The feedback generator plays a significant role by assessing the impact of the optimized drug doses and adjusting them to ensure the desired number of normal cells. The system incorporates a comprehensive cell-cycle-specific model to monitor relevant parameters throughout chemotherapy. Extensive simulations and comparative assessments with existing computational models validate the superior effectiveness of our proposed approach over other methods reported in related studies.**

***Index Terms*—Cell-cycle specific scheduling, Feedback, Multi-objective particle swarm optimization, Cancer Chemotherapy**

I. Introduction

Chemotherapy is a crucial part of cancer treatment because it has a unique ability to neutralize cancer by slowing its progression and causing the death of cancer cells [1]. However, carefully administering chemotherapy doses is important to maintain a trade-off balance between its anti-cancer effects and the potential impact on normal cells [2]. Achieving a balance between optimizing treatment outcomes and minimizing harm to healthy cells is very important. Proper drug dose scheduling plays an essential role in achieving this balance. The most effective scheduling of chemotherapy drug dose can provide a consistent treatment plan, minimizes potential adverse effects, and increases the drug's effectiveness [2].

The combination of compartmental models and cell cycle-specific chemotherapy has proven to be highly effective in the treatment of cancer. These approaches offer valuable insights into the distribution and elimination of drugs within the body, facilitating the development of optimal dosing strategies [3]. Targeting cancer cells during sensitive steps of the cell cycle enhances treatment outcomes and reduces side effects [4]. Moreover, the integration of multi-objective optimization algorithms has contributed significantly to the field of cancer chemotherapy dose scheduling [5]. It simultaneously considers multiple objectives and constraints, enabling the identification of optimal treatment regimens. These regimens aim to achieve various goals, including maximizing tumor control and minimizing toxicity to healthy cells while also taking into account patient-specific constraints [5], [6].

This research presents a novel approach for scheduling optimal cell cycle-specific chemotherapy doses, combining a multi-objective optimization algorithm with a feedback generator-based system. Feedback is essential in cancer chemotherapy dose scheduling as it enables the adjustment and optimization of treatment regimens based on individual patient responses, considering physiological indicators, tumor progression, and drug toxicity levels. In contrast to existing approaches that only depend upon suggested doses without considering after-effects, this method incorporates feedback on the suggested dose obtained from the multi-objective optimization algorithm. The dose is subsequently adjusted based on this feedback, resulting in an enhanced dosing strategy that maximizes therapeutic outcomes while minimizing side effects.

Among the remaining sections, Section II presents and discusses recent research regarding chemotherapy scheduling, Section III describes the feedback generator-based MOPSO,

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and Section IV delineates the obtained results. Finally, in Section V, this research concludes with the findings.

II. Literature Review

To calculate the meticulous amount of drug dose and optimal chemotherapy dose scheduling, numerous optimization methods have been utilized. These techniques include parameterization and analytical gradient methods [7], cell-cycle-specific mathematical models [8], genetic algorithms (GA) using adaptive elitist populations [9], distributed evolutionary control algorithms [10], and memetic algorithms [11]. These methods used open-loop control procedures to provide the optimal drug doses, which shows the incapability of controlling the drug dose accurately, leading to ineffectiveness in treatment outcomes. To address this issue, researchers have implemented closed-loop control of drug concentration in chemotherapy by introducing schedulers based on Proportional-Integral-Derivative (PID) control using multi-objective particle swarm optimization (MOPSO) and genetic algorithm (GA) [12], [13]. Further, by adopting multi-objective genetic algorithm (MOGA) oriented I-PD control systems for cancer treatment, Alam et al. [4] have enhanced and expanded these methods.

In recent years, a variation of PID controllers has been introduced in [14] (2FOPID), where multi-objective optimization algorithms are used to adapt the parameters and to improve the robustness of the controller. In this field, alternative approaches such as the utilization of the fuzzy logic controller [15], reinforcement learning-based control [16], and modular fuzzy expert system-based method [2] have been implemented for the management of anti-cancer drug delivery systems.

Furthermore, multi-objective particle swarm optimization (MOPSO) is an effective and adaptable optimization algorithm, outperforming other nature-inspired algorithms in various domains [17]. It requires fewer parameters to tune and has gained popularity due to its successful applications in networking, robotics, power generation, fuzzy systems, and more [17], [18]. MOPSO's capability to hybridize and specialize allows it to exhibit emergent behaviors, making it a valuable tool in diverse fields.

III. Proposed Methodology

This section illustrates the methodology for determining the optimal schedule for administering drugs to cancer patients. The approach involves utilizing a two-compartment model designed explicitly for cell cycle-specific chemotherapy. Additionally, we propose a feedback generator-based MOPSO for computing the optimal drug dose. The feedback generator-based MOPSO is responsible for determining the appropriate amount of drug dose. Further, this provided dose and cell cycle-specific mathematical model calculates vital measurements such as the number of cancerous and healthy cells, drug concentration, and toxicity. To visualize the overall process, the proposed system of the optimal scheduler is depicted in Fig. 1.

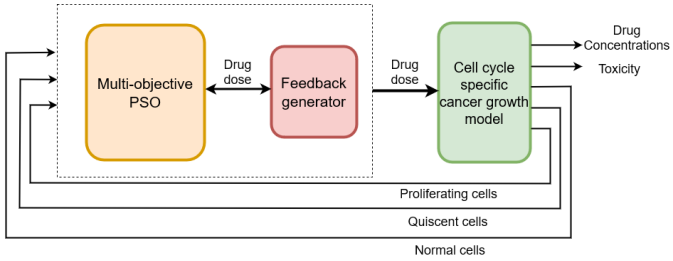

Fig. 1. Proposed architecture of the optimal scheduler.

A. Cell cycle specific compartmental model

The cell cycle encompasses steps that healthy and cancerous cells progress through from formation to demise. These phases can be represented using compartments that describe distinct cell-dividing stages or groups of stages into clusters. The cell cycle typically encompasses five stages, as depicted in Fig. 2, where the proliferating compartment (pre-DNA synthesis (G1), synthesis (S), pre-mitosis (G2), and mitosis phase (M)) consists of actively dividing cells in a cycling state. In contrast, the quiescent (resting phase (G0)) population comprises cells in a resting state that have the potential to proliferate later in the life cycle [8].

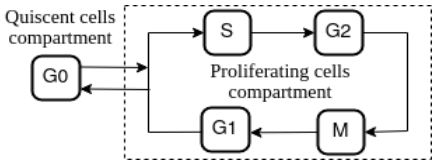

Fig. 2. Cell cycle specific compartmental model.

Considering this two-compartmental model, we employed five differential equations [8], [19], which study both cancerous and normal cells of the patient's body. According to clinical studies, at the beginning of the treatment, the proliferating and quiescent cell compartment contains 20% and 80% cells of 10^{12}, respectively [8]. The applied cytotoxic drugs can kill both cancerous and normal cells, so this research also considers normal cells 10^9. This patient's related parameters can be calculated based on the tumor's size on a patient's body [8]. The differential equations are as follows [8], [19]:

$$\frac{dP}{dt} = (a-b-c)P(t) + dQ(t) - g(t)P(t) \tag{1}$$

$$\frac{dQ}{dt} = cP(t) - (d+e)Q(t) \tag{2}$$

$$\frac{dM}{dt} = \delta(1 - \frac{M(t)}{K})M(t) - g(t)M(t) \tag{3}$$

$$\frac{dD}{dt} = U(t) - \gamma D(t) \tag{4}$$

$$\frac{dg}{dt} = \lambda D(t) \tag{5}$$

In these equations, the proliferating cells, quiescent cells, and normal cells are represented as P(t), Q(t), and M(t). Equation

(1), (2), and (3) illustrates the impact of administrative drug on both cancerous and normal cells. Further, the change of drug concentration in the patient's body is calculated by (4) and (5) to identify the drug's destructive impact [8]. Moreover, considering the Docetaxel drug as a medication, all the associated parameters are delineated in Table I.

TABLE I
PARAMETRIC SETTINGS OF CELL-CYCLE-SPECIFIC CHEMOTHERAPY [4]

Parameter	Description	Value
a	Proliferating cell growth rate	0.5 $day^{-}1$
b	Death rate of dividing cells naturally	0.477 $day^{-}1$
c	Proliferating to quiescent cells transition	0.218 $day^{-}1$
d	Quiescent to proliferating cells transition	0.05 $day^{-}1$
e	Quiescent cells death rate naturally	0.0173 $day^{-}1$
μ	Toxicity removal rate	0.4 $day^{-}1$
γ	Docetaxel's rate of decay	0.25 $day^{-}1$
λ	Effect of docetaxel on cell death per unit of drug concentration	0.0092 $day^{-}1$
δ	The frequency of healthy cell development	0.1 $day^{-}1$
$D_i(t)$	Drug concentration	mg/ml
$U_i(t)$	Drug dose	Mg/ml $day^{-}1$

B. Feedback generator-based multi-objective optimization

1) MOPSO: Here, MOPSO is utilized to determine the optimal drug dose. This approach is chosen due to its ability to converge towards near-optimal solutions. Additionally, it is known for its simplicity in implementation, requiring a few parameters, and being computationally efficient [1]. The proposed MOPSO typically follows the following basic steps [22]:

1) Initialization of various parameters (number of particles, number of generations, upper and lower bounds of variables, and other constants).
2) Randomly initialize positions and velocities of the particles within the specified bounds.
3) The fitness values for each particle are evaluated using the feedback generator-based objective function. Particle's position is also adjusted based on feedback.
4) The best performance and corresponding position are initialized as the fitness value and position of the particle with the minimum cost.
5) The velocities and positions of the particles are updated based on the current positions, velocities, personal best positions, and the global best position calculated from the feedback generator-based objective function.
6) Update the best position and the global best position.
7) Repeat steps 5 and 6 until the termination criterion is met. The final position matrix represents the optimal drug dose.

2) Feedback generator-based objective function: The effects of administering a drug dose intravenously to a patient are significant, especially when the quantity of normal cells correlates closely to the lowest point of the normal cell population (also known as a lower limit of normal cells, 10^8). If a large dose of the drug is applied, it is anticipated that the population of normal cells will temporarily fall below 10^8 for the next two to three days. However, based on the growth rate of normal cells described in Table I, the normal cell population will rapidly recover to 10^8 or higher within two or three days of drug administration. This situation is not desirable for an optimal chemotherapy scheduling system.

So, this proposed feedback generator is designed to calculate the daily normal cell numbers before administering the drug dose to the patient's body. It utilizes a cell-cycle-specific mathematical model as the objective function and receives each dose provided by the MOPSO algorithm. To predict the after-effects, the feedback generator will calculate the normal cell numbers for each day up to the seventh day before administering the drug dose to the patient. The feedback generator will output the minimum normal cell number observed among the calculated values for each day up to the seventh day. Suppose the minimum normal cell number is equal to or falls below the normal cell threshold (a parameter that can be adjusted according to user preferences, such as 1.1×10^8, 1.4×10^8, 1.7×10^8, etc.). In that case, the feedback generator recommends reducing the drug dose by a certain percentage (e.g., 10% , 20% , etc.). The specific percentage of dose reduction will depend on the user's preferences, and the impact of the reduction is thoroughly described in the result analysis section (Section IV).

The feedback generator employs (3), (4), and (5) to compute the dose concentration, the cell-kill effect of the drug (docetaxel), and the normal cell number in the individual's body.

C. Objectives and constraints

Following are the constraints and parameters used for performance measurement in this proposed chemotherapy medication scheduler:

- Initial proliferating cells are 2×10^{11} [8].
- Initial quiescent cells are 8×10^{11}, as stated in [8].
- The amount of healthy cells must be as high as feasible during the entire course of treatment. According to other studies [4], [8], the lowest allowable value for healthy cells is 10^8 ($M(t) > 10^8$).
- The planned chemo dose for injecting into the individual patient's body must have to be in the tolerated range ($0 \leq U(t) \leq 50$) [4], [8], [19].
- The total treatment period is 86 consecutive days.
- A fixed interval of 7 days has been applied for normal cell recovery.
- Normal cell threshold can be set according to the user's preference (e.g., 10^8).
- The drug dose adjustment percentage by which the drug dose will be modified if the normal cell population falls below the threshold (e.g., 15%).

The design objectives are as follows:

- Total cancerous cell: The first goal of the proposed scheduler is to maximize the effectiveness of the chemotherapy

treatment by reducing the total cancerous cell number after 86^{th} day.

$$Objective1 : Z1 = P(t) + Q(t) \tag{6}$$

- Total normal cell: The second goal is to reduce the impact on normal cell populations.

$$Objective2 : Z2 = \int_0^{86} (10^9 - M(t)/dt) \tag{7}$$

IV. Result Analysis

In the implementation and simulation tests of our multi-objective PSO and feedback-based chemotherapy drug dose scheduler, we utilized the MATLAB R2020a software. The simulation was conducted over a total duration of 86 days, with a sampling interval of 1 day, following standard practice. Section III-C provides a comprehensive and detailed description of all the objectives, constraints, and parameters utilized in our proposed approach.

The optimization process involves the use of 50 particles and 50 iterations to collectively explore and search for the optimal solution within the search space. The particle positions, representing the amount of drug dose, are constrained within a range of 15 to 23 units. The threshold for normal cell count is set at 8.2×10^8, and a drug dose adjustment percentage of 20% is employed, both of which can be adjusted based on user preferences and the patient's health condition (Section III-C).

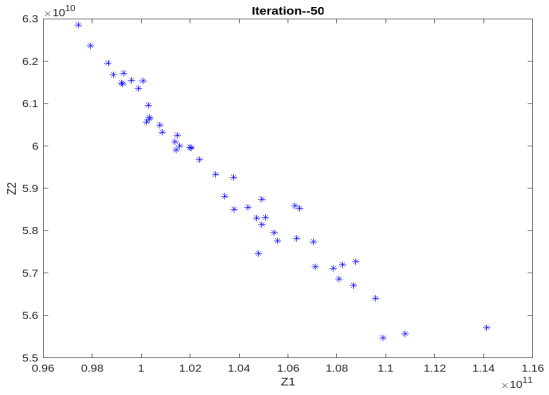

Fig. 3. Pareto font for optimal solutions.

Throughout the simulation period of 86 days, the tumor burden parameters are continuously monitored. After completion, the multi-objective optimized drug regimens are visualized in the objective space as depicted in Fig. 3, which is the overview of the optimized solutions achieved by the proposed system.

The main goal of this study is to achieve an optimally designed schedule that effectively reduces the maximum tumor burden. Here, a fixed interval (7 days) variable dose approach is adopted, where the time between consecutive chemotherapy treatments remains constant throughout the treatment phase. Through the optimization process, it has been seen that, obtained schedules ensure more than the minimum level of normal cells sustained at the end of the treatment.

Fig. 4 illustrates the selected drug schedule, highlighting the specific doses and timing for each administration. Additionally, the associated medication concentration in the individual's body following the administration of this optimized plan is shown in Fig. 5. This information helps to assess the effectiveness and distribution of the drug within the patient's body.

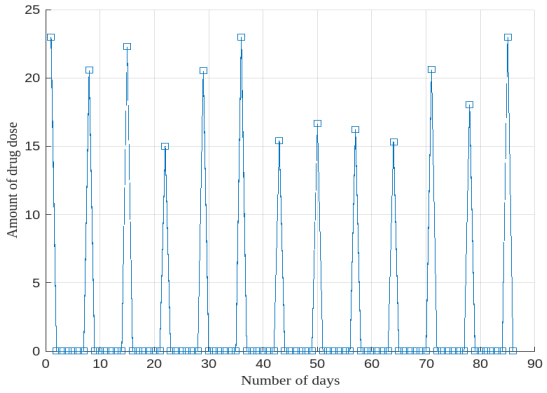

Fig. 4. Obtained optimal chemotherapy dose schedule for 86 days.

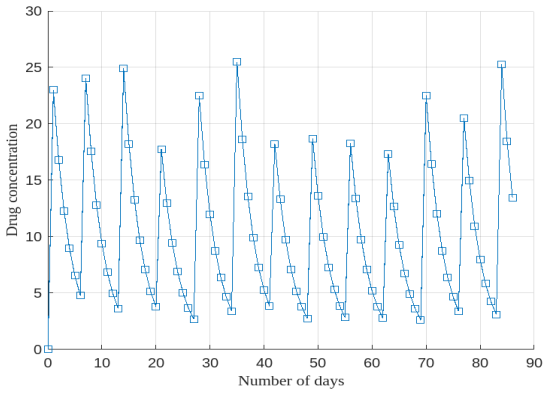

Fig. 5. Drug concentration by applying the optimal chemotherapy dose.

Reducing cancerous cells (proliferating and quiescent cells) is one of the major objectives of optimal chemotherapy treatment, as these cell types have the potential to expand cancer to key organs. By applying our selected schedule, the reduction of cancerous cells throughout the entire treatment period is presented in Fig. 6 and 7. Moreover, Fig. 6 and 7 illustrate the reduction of proliferating cells and quiescent cells, respectively, where the significant decrease of cancer cells over the course of 86 days is clearly evident.

At the last of the treatment, there are about 1.5×10^{10} proliferating cells left, a decrease of 92.34%. Similarly, the number of remaining quiescent cells is estimated to be around $8.6 \text{x} 10^{10}$, indicating an 89.15% reduction. Collectively, these reductions in both cell types contribute to an overall reduction of 89.9% in the tumor burden.

As the cytotoxic drug doesn't only kill cancerous cells, it also has a negative impact on healthy cells, which is illustrated in Fig. 8. It represents the effect of the drugs on the population

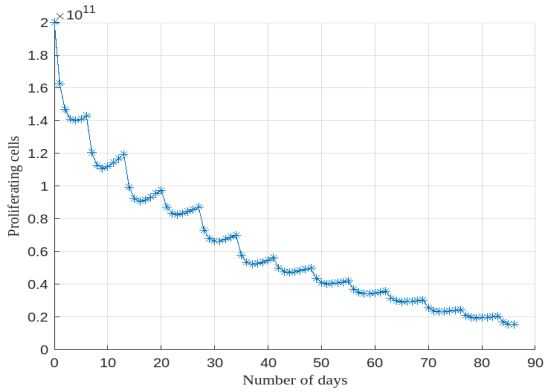

Fig. 6. The impact of optimal chemotherapy dose schedule on proliferating cells.

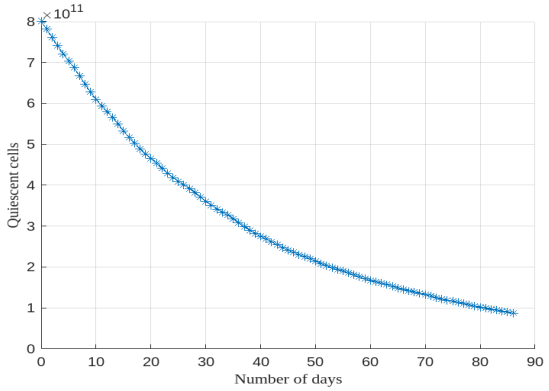

Fig. 7. The impact of optimal chemotherapy dose schedule on quiescent cells.

of healthy cells over the course of treatment. Despite the presence of toxicity, the treatment strategy employed ensures that a substantial number of healthy cells survive. At the end of the treatment, the estimated count of surviving normal cells is 1.842×10^8 cells, demonstrating the effectiveness of the optimized chemotherapy in preserving the health and integrity of normal cell populations.

According to Section III-C, the dose decrease percentage and normal cell threshold can be set based on the user's preferences, which can play a significant role in killing cancerous cells. The impact of dose decrease percentage and normal cell threshold on cancerous cells is demonstrated in Fig. 9 and 10. By analyzing Fig. 9, it becomes clear that a 10% dose decrease results in higher destruction of proliferating cells compared to reductions of 15%, 20%, 25%, or 30%. As the dose decrease percentage increases, the rate of proliferating cell destruction diminishes, with 30% dose reduction causing the least amount of proliferating cell fatalities among the tested percentages. By examining Fig. 10, it becomes evident that a higher normal cell threshold value corresponds to a lower impact on cancerous cells. Conversely, decreasing the threshold value intensifies the effect on these cell populations.

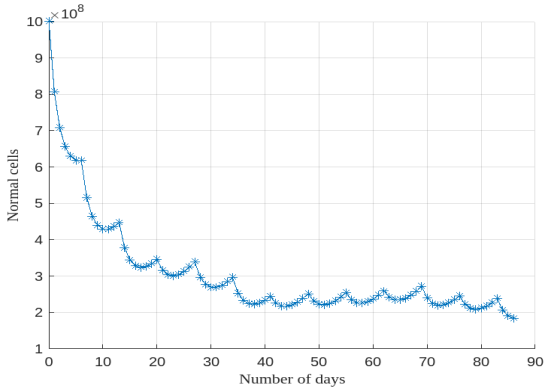

Fig. 8. The impact of optimal chemotherapy dose schedule on normal cells.

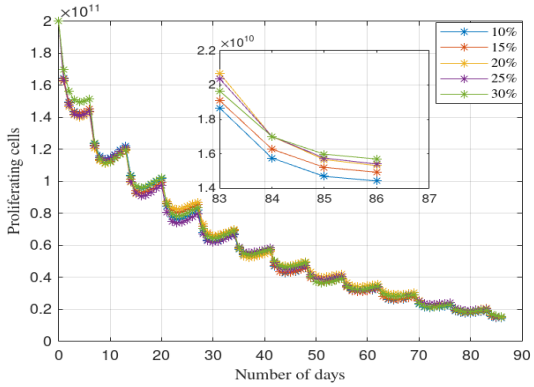

Fig. 9. Sensitivity analysis of dose decrease percentage on proliferating cells.

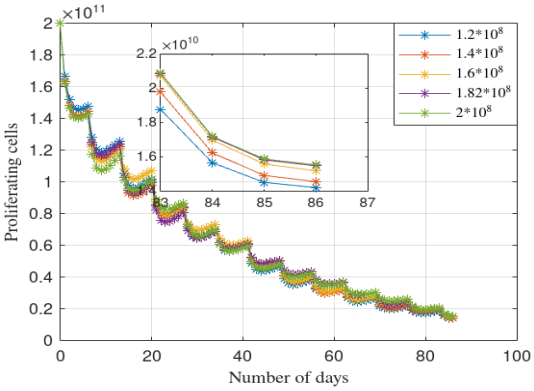

Fig. 10. Sensitivity analysis of normal cell threshold on proliferating cells.

Further, a comparison of the proposed approach's effectiveness with other optimal control techniques applied in earlier research with related goals is shown in Table II. The evaluation is based on several key metrics, including the percentage decrease of proliferating and quiescent cells and the number of healthy cells remaining after 86 days of treatment.

This outcome indicates that the proposed approach performs far better than the alternative approaches to treat cancer. Among the recent studies, [4], [8], [12], [14], [21] achieved low performance which is less than 73% reduction in proliferating cells and 62% in quiescent cell reduction. At the same time, they were able to preserve too little amount of normal

TABLE II
COMPARATIVE ANALYSIS OF THE EFFECTIVENESS OF THE PROPOSED APPROACH AND THE STATE-OF-THE-ART CHEMOTHERAPY DRUG SCHEDULING TECHNIQUES.

	% reduction in P cells	**% reduction in Q cells**	**Number of Normal cells**
Proposed method	92.34	89.15	1.842×10^8
Panjwani et al. [20]	90.25	87	1.8×10^8
Nikhil et al. [14]	71.9	57	1.03×10^8
Dua et al. [8]	70	50	1.05×10^8
Pachauri et al. [21]	72.4	60.5	1.009×10^8
Algoul et al. [12]	72.5	61	1.03×10^8
Alam et al. [4]	72.2	60.4	1.0002×10^8

cells which is very alarming for the patient's health. The reason for their inferior performance is much focus on controller parameter optimization rather than drug dose optimization, and not applying fixed interval dose schedules. Though Panjwani et al. [20] achieved the second-best outcome, it was not able to surpass the proposed method's performance because of not considering any feedback mechanisms.

However, our proposed approach exhibits the highest percentage reduction in both proliferating (92.34%) and quiescent cells (89.15%), indicating its effectiveness in suppressing the growth and spread of cancerous cells. Additionally, the proposed approach excels in preserving more normal cells (1.842×10^8) than the alternative methods.

V. CONCLUSION

In this research paper, we have introduced a novel process for optimizing chemotherapy treatment through a MOPSO and a feedback generator-based drug dose scheduler. Our study aimed to reduce the maximum tumor burden while minimizing toxicity and preserving normal cell populations. Through comprehensive simulations and evaluations, we have demonstrated the effectiveness and superiority of our proposed approach. The optimized treatment schedules significantly reduced proliferating and quiescent cancer cells, thereby mitigating the risk of cancer spreading to major organs. Additionally, a substantial number of normal cells were preserved, emphasizing the importance of minimizing treatment-induced damage to healthy tissues. As demonstrated by a comparative analysis, our proposed methodology performed better than other optimal control techniques used in earlier research. The reduction percentages attained and the number of healthy cells that survived after 86 days are higher than those of different methods, demonstrating the exceptional effectiveness of our strategy in accomplishing the objectives of cancer treatment.

However, to get assurance from our proposed MOPSO and feedback-based model requires experiments in an in-vivo lab before this approach is applied in the clinic. So, in the future, research on clinical validation, combination therapies, and integration of pharmacokinetics and pharmacodynamics can be incorporated to enhance the effectiveness and applicability of chemotherapy scheduling models.

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